Review Article

Endoscopic bronchial ultrasound in mediastinal staging of lung cancer

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Abstract

Lung cancer is a global healthcare concern with a low 5-year survival rate and a high proportion of advanced-stage cases at diagnosis. In the absence of distant metastasis, the most important prognostic marker is mediastinal lymph node involvement. Timely diagnosis and staging improves prognosis, making rapid, safe, and accurate investigation essential.

Endoscopic bronchial ultrasound (EBUS) is a minimally invasive technique which allows for ultrasound-guided transbronchial needle aspiration (TBNA) during bronchoscopy, with cytological sampling of several intrathoracic groups of lymph nodes. EBUS reduces need for open surgical biopsy, with good sensitivity and specificity and excellent safety profile.

This article reviews current evidence regarding use of EBUS in lung cancer staging, including its role in other intrathoracic malignancies.

MeSH terms

ebus, lung cancer, nsclc, staging, lymphadenopathy

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Introduction

Despite advances made in oncology and aggressive anti-smoking public health campaigns, lung cancer remains a significant burden in terms of patient morbidity and mortality. 2012 saw an estimated 1.6 million deaths worldwide from the disease, and incidence is increasing, with a projected 3 million fatalities predicted in 2035, mainly in the developing world.[1] Especially of concern is the fact that average 5-year survival for all kinds of lung cancer is as low as 10-20%, with little variation in prognosis between developed and developing regions.[2] The local data is similarly bleak: incidence of lung cancer in Malta is on the rise, especially in women – and it is associated with an even more worrying increase in mortality.[3]

Lung cancer can be divided into small cell and non-small cell lung cancer, the former accounting for around 20% of cases and carrying a worse prognosis due to its usual late stage and inoperability on diagnosis.[4] Comparatively, 48% of non-small cell lung cancer patients in the UK have stage IV disease on diagnosis,[5] but keeping in mind that early stage I disease has a 72.5% 1-year survival rate, the importance of rapid diagnosis and staging is highlighted.

The most widespread staging classification in use for lung cancer is the TNM staging system, shown in table 1.[6] Nodal status is the most important prognostic marker in the absence of metastatic disease, as only patients with N0, N1 and very selected cases of N2 disease are amenable to surgery, which is the definitive curative treatment.[7] If surgery is not an option, patients should be referred for chemotherapy, radiotherapy, or a combination, with the intent of cure or palliation.[8] Thus, accurate nodal staging is crucial to guide the best possible selection of treatment.

Conventional staging of lung cancer had so far included the use of CT, PET-CT, radiology-guided transthoracic biopsy and flexible bronchoscopy to determine extent of disease. Some centres offer mediastinoscopy under general anaesthesia. This is

available in the Maltese healthcare system, but is falling out of favour due to its invasive nature. However, there is significant delay, unnecessary investigation, and cost burden associated with multiple tests,[9] and this creates a niche for an investigation that can provide extensive information at one go. Since its introduction in 1992, endoscopic bronchial ultrasound (EBUS) has become increasingly useful in this regard, providing excellent information with regard to both diagnosis and staging of lung cancer in one procedure. This year marks the introduction of EBUS in the Maltese healthcare system, with expected benefits in investigation of malignant and benign conditions alike.

Table 1: *TNM staging (Adapted from TNM7 staging system[6])*

Primary tumour (T)	
TX	Primary tumour cannot be assessed, or the tumour is proven by the presence of malignant cells in sputum or bronchial washing but is not visualised by imaging or bronchoscopy
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour ≤ 3cm in greatest dimension, surrounded by lung or visceral pleura, no bronchoscopic evidence of invasion more proximal than the lobar bronchus (not in the main bronchus)
T1a	Tumour ≤ 2 cm in greatest dimension
T1b	Tumour > 2 cm but ≤ 3 cm in greatest dimension
T2	Tumour > 3 cm but ≤ 7 cm or tumour with any of the following: - Invades visceral pleura - Involves the main bronchus ≥ 2 cm distal to the carina - Associated with atelectasis/obstructive pneumonitis extending to hilar region but not involving the entire lung
T2a	Tumour > 3 cm but ≤ 5 cm in greatest dimension
T2b	Tumour > 5 cm but ≤ 7 cm in greatest dimension
T3	Tumour > 7 cm or one that directly invades any of the following: chest wall (including superior sulcus tumours), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, parietal pleura Or tumour in the main bronchus < 2 cm distal to the carina but without involvement of the carina Or associated atelectasis/obstructive pneumonitis of the entire lung or separate tumour nodule(s) in the same lobe.
T4	Tumour of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, or carina; or separate tumour nodule(s) in a different ipsilateral lobe
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in the ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in the contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumour nodule(s) in contralateral lobe; tumour with pleural nodules or malignant pleural/pericardial effusion
M1b	Distant metastasis

Endoscopic bronchial ultrasound

EBUS allows for real-time visualisation of the bronchi, mediastinum, and lung parenchyma using an ultrasound probe attachment during flexible fibreoptic bronchoscopy. The concept of concurrent endoscopy and ultrasonography is not limited to bronchoscopy; the use of endoscopic ultrasound (EUS) for the gastrointestinal tract is established and has also been introduced in Malta.[10] Together, these two counterparts provide access to good-quality imaging and biopsy of mediastinal lymph nodes previously only achievable with invasive surgical staging.

There are a large variety of EBUS probes available on the market, but these can be broadly classified into radial probes (RP-EBUS) and convex probes (CP-EBUS). Radial probe EBUS has the advantage of higher-resolution (20-30MHz) circumferential imaging with better distal access. On the other hand one cannot perform real time ultrasound during biopsy using this technique.[11] Conversely, CP-EBUS (figure 2) is a larger, lower-frequency 7.5MHz probe with better interventional utility, as transbronchial needle aspirations (TBNA) can be carried out with concurrent ultrasound guidance, improving safety profile and diagnostic yield compared to blind TBNA.[12]

Figure 2: *Convex-probe EBUS*

Convex-probe EBUS-TBNA technique

EBUS is carried out as a day procedure under conscious sedation or general anaesthesia. Contraindications to the procedure are few and similar to those of conventional bronchoscopy, summarised in table 2. Because of a theoretical risk of bleeding during TBNA, the current practice is to withhold antiplatelet agents and anticoagulants prior to the procedure.[13] By convention, aspirin and warfarin are stopped for three days pre-procedure, with bridging heparin for warfarinised patients for whom omission of warfarin is contraindicated, and clopidogrel is stopped one week prior.

Table 2*: Contraindications to EBUS-TBNA*

Contraindications to EBUS-TBNA
Current or recent myocardial ischaemia
Severe hypoxaemia
Haemodynamic instability
Severe pulmonary hypertension
Poorly-controlled heart failure
COPD/asthma exacerbation
Life-threatening dysrhythmias
Patient on anticoagulation/antiplatelets (not stopped)
Clotting abnormalities
Intolerance to sedation/anaesthesia

During the procedure, potentially malignant lymph nodes can be identified by the following characteristics: round shape, heterogeneous echogenicity, distinct margin, presence of coagulation necrosis sign (a hypoechoic area within an enlarged node showing absence of Doppler signal).[14] Absence of all four features carries a 96% chance that the visualised node is benign. Once a potentially abnormal node is identified, this may be biopsied with a retractable 21 or 22 gauge needle introduced through the bronchoscope. The needle is then used to puncture the bronchial wall and pierce the suspicious node under ultrasound guidance. Suction is applied to obtain a cytology specimen, with at least three punctures per lymph node recommended to maximise yield,[15] following which the needle is retracted. The procedure can be repeated for other abnormal nodes as needed.[11]

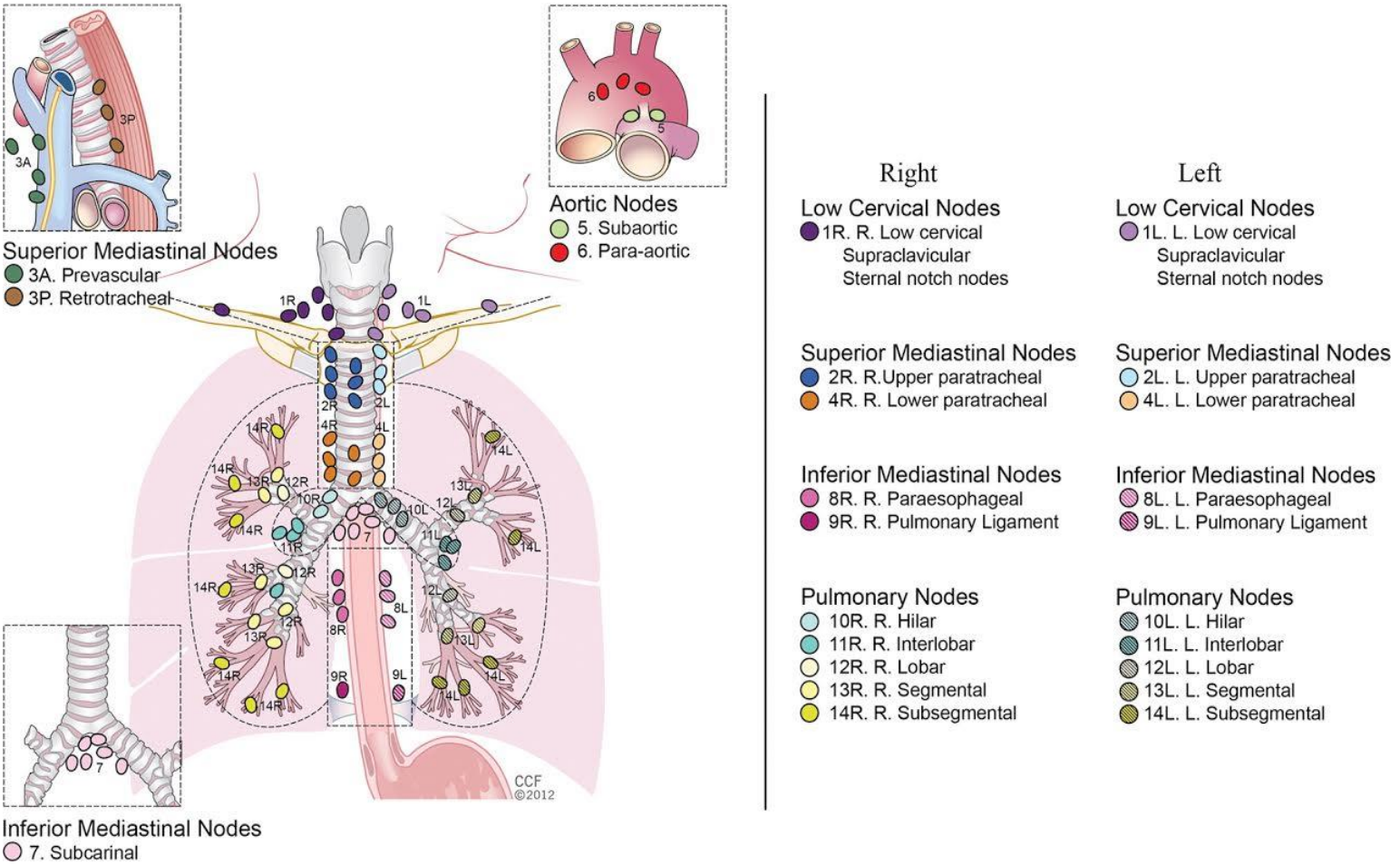
The specimen obtained from EBUS-TBNA is a cytology specimen, which is handled in liquid fixative like conventional TBNA or transthoracic needle biopsy samples. In order to maximise tissue yield, manufacturers are developing new needles for

use in difficult-to-diagnose pathology such as lymphomas or rare cancers.[16] Despite the current unavailability of histology specimens from EBUS-TBNA, much information can be obtained from good-quality samples. A retrospective, multicentre study of 774 patients showed that 90% of EBUS-TBNA samples were suitable for endothelial growth factor receptor (EGFR) testing and 77% were sufficient for subtyping with staining and immunohistochemistry.[17]

Some specialised centres also offer rapid on-site evaluation (ROSE) for EBUS-TBNA specimens, with review of samples during the procedure for e. While there are no current clinical trials available, several smaller-scale studies have reported that ROSE increases diagnostic yield in a cost-effective manner, with less strain on the pathology service due to insufficient samples.[18-20]

Examination of lymphadenopathy during EBUS requires a good working knowledge of the anatomy of cervical and intrathoracic lymph nodes. The current convention is the International Association for Study of Lung Cancer (IASLC) lymph node map, published in 2014,[21] seen in figure 1. The system describes 14 lymph node groups, or stations in the neck and chest, categorised into 7 zones, which may be involved in local and regional spread of lung cancer.

***Figure 1**: Reproduced from IASLC mediastinal lymph node map[21]*



It is important to note that, while EBUS provides excellent access to certain lymph node stations, it is not technically possible to gain access to all of them, and other techniques such as EUS may be required to access lower thoracic stations. Table 3 summarises lymph node stations accessible to different investigation modalities.[22]

Keeping in mind that different procedures access different nodes, there is an increasing question as to whether EBUS and EUS should be performed together in order to maximise accuracy and completeness of staging. A 2015 meta-analysis of 10 studies with 1080 participants showed that combination EUS and EBUS showed a significantly higher sensitivity for staging of lung cancer of 91% compared to 80% in EBUS alone, without significant increase in complication rate.[23,24]

However, this raises some concern as to

whether such extensive investigation is necessary in all cases. A 2010 US study used software models to compare cost-effectiveness between combined EUS-EBUS and EUS alone and reported that combining the two procedures is more cost-effective in cases where there are enlarged mediastinal lymph nodes on CT, while absence of lymphadenopathy favours the use of EUS alone.[25]

***Table 3**: Access to lymph node stations by procedure*[22]

Station	EBUS	EUS	Mediastinoscopy	Video-assisted thoracoscopic surgery (VATS)[a]
1 – Low cervical, supraclavicular, sternal notch	*		*	
2 – Upper paratracheal	*	*	*	
3 – Prevascular, retrotracheal	*	*		*
4 – Lower paratracheal	*	*	*	*
5 – Subaortic		*	* [b]	
6 – Para-aortic		* [c]	* [b]	
7 – Subcarinal	* [d]	* [e]	*	*
8 – Para-oesophageal		*		*
9 – Pulmonary ligament		*		*
10 – Hilar	*			*
11 – Interlobar	*			
12 – Lobar	*			
13 – Segmental				
14 – Subsegmental				

[a] Unilateral access only
[b] Extended mediastinscopy only
[c] Requires trans-aortic biopsy
[d] Anterior subcarinal nodes
[e] Posterior subcarinal nodes

Which investigations to use for staging?

The 2014 Scottish Intercollegiate Guidelines Network (SIGN) guidelines for management of lung cancer states that a CT scan of the thorax and abdomen should be requested in patients with suspected lung cancer regardless of chest X-ray result. Chest CT is regarded as being positive for mediastinal lymphadenopathy with nodal size >10mm short axis diameter. However, the guideline acknowledges the high false positive and negative rates for diagnosing abnormal nodes on CT (45 and 13% respectively)[26] and recommends use of PET-CT scan in patients being staged before radical treatment, which has the benefit of a low false negative rate of 5%.[26] Patients with >10mm nodes on CT and/or positive uptake of FDG on PET should be considered for mediastinal nodal sampling for definitive staging, as combined PET and CT have sensitivity of 61% and specificity of 96% for positive mediastinal nodes.[27] The guideline recommends the use of EBUS-FNA with or without EUS-FNA for endoscopic assessment of suspected mediastinal involvement prior to mediastinoscopy.[26]

Prior to EBUS gaining popularity, surgical staging with mediastinoscopy was regarded as the gold standard investigation of possible metastatic mediastinal lymphadenopathy, but this is changing.[28,29] This day procedure involves the insertion of a rigid mediastinoscope through the suprasternal notch under general anaesthesia, with direct visualisation of the upper mediastinum and biopsy of abnormal tissue. However, increasing evidence backs the use of endosonography prior to invasive surgical staging, and one of the most important contributions is the 2010 ASTER trial. This shows that combination EUS/EBUS, followed by surgical staging if negative, prevents unnecessary thoracotomy in 1 in 7 patients compared to immediate surgical staging, with

similar sensitivities between the two arms (85% in endosonography versus 79% in mediastinoscopy) and reduced risk of complications in the endosonography (1% versus 6% in mediastinoscopy group).[30]

These findings, coupled with the fact that combined EBUS and EUS are still more cost-effective than mediastinoscopy,[25] would lead one to believe that mediastinoscopy has no further role in staging of lung cancer. However, there is much controversy about the value of a negative EBUS, with varying negative predictive values available in the literature, especially for central tumours.[31-33] The present consensus is that mediastinoscopy should be considered in cases of negative EBUS, but is not an essential step prior to proceeding to thoracotomy; further research is needed to clarify mediastinoscopy's role in modern lung cancer staging.

Perhaps one of the greatest endorsements for EBUS has been the 2015 BOOST trial comparing standard staging investigations, as would be seen in a non-endosonography centre (such CT, PET-CT, conventional bronchoscopy, mediastinoscopy, CT-guided biopsy), with the use of EBUS or EUS immediately following CT. The use of endosonography as an initial investigation was shown to reduce time from first outpatient contact to treatment decision by multidisciplinary team from 29 days to 14, and the EBUS/EUS group was noted to have a lower mean number of investigations per patient, unnecessary thoracotomies, and PET-CT scans. Both groups had the same number of patients being treated with curative intent, but EBUS was shown to be faster, less costly, and – following a post-hoc analysis of patient survival – associated with better post-operative survival compared to patients staged conventionally.[17]

EBUS in small-cell lung cancer

Most studies on EBUS discuss its use in NSCLC due to its better amenability to surgery, but the limited data available on small-cell lung cancer appears promising. In a retrospective analysis of 161 patients, use of EBUS for suspected SCLC showed sensitivity and specificity of 97.4% and 100% respectively, with a negative predictive value of 60%[34], echoing the findings of similar retrospective studies.[35,36] However, the fact that SCLC is often non-resectable at diagnosis often precludes the use of EBUS for workup, making its role not as well-defined as in other tumours.

EBUS in lymphoma

The role of EBUS in lymphoma is highly controversial and guidelines do not currently recommend its use in suspected lymphoma cases.[37] Extensive data is limited but there is concern about high false negative rates, especially in Hodgkin's lymphoma.[38] Sensitivity data is variable but values range from 38%[39] to 86.7%.[40] Much of the problem centres around the fact that accurate diagnosis and subtyping of lymphoma requires histological samples, ideally with excisional biopsy.[41] In fact, the use of ROSE is thought to be beneficial to improve diagnostic yield in lymphoma.[42] There is also a large variability in the design and selection of patients studied, with recurrent cases often being grouped with suspected lymphoma patients, making meta-analysis difficult to design.

EBUS in metastatic extrathoracic disease

EBUS may also be an option for investigation of mediastinal lymphadenopathy in the context of extrathoracic malignancies. A 2014 meta-analysis of 533 patients showed that pooled EBUS-TBNA sensitivity and specificity were 85% and 99% respectively, indicating diagnostic accuracy similar to that in NSCLC.[34] Furthermore, EBUS is capable of delivering samples sufficient for immunohistochemistry and molecular analysis in around 80% of cases.[43]

Conclusion

Although there are still gaps in available evidence, the use of EBUS, with or without EUS, for mediastinal lymph node staging is safe, fast, accurate, and cost-effective. EBUS shortens the time to diagnosis whilst ensuring that patients are staged accurately and referred for the appropriate treatment. Large-scale trials are needed to confirm the usefulness of EBUS in small-cell lung cancer and metastatic extrathoracic malignancy, but the future for this investigative modality appears bright.

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